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Oral antineoplastic agents: how do we care about adherence?

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AIMS

Oral therapies, including hormone-based or targeted therapies, have recently taken an increasing place in cancer treatment. In this context, a state of the art of the available studies dealing with the adherence of adult patients to oral anticancer treatment is warranted. The purpose of this review is to address (i) the association between assessment methods and measured adherence, (ii) the putative factors related to adherence and (iii) new ways of improving adherence to oral cancer therapies.

METHODS

We conducted a literature-based narrative review of studies obtained from Pubmed using medical subject heading terms and free-text terms combining concepts related to oral anticancer medication and adherence.

RESULTS

The analysis is based on 48 studies published since 1990, mostly assessing hormone-based therapy in breast cancer and targeted therapies in chronic myeloid leukaemia. Various methods of adherence were reported including self-report, medication measurement or combinations of methods. Adherence rates were found to vary from 14% to 100%. Beside patient related-factors, adherence rate discrepancies were found to be dependent on the method used. Furthermore, there was no consensual definition of adherence even regarding the same methods, some of them tolerating a period of interruption during the treatment period. Finally, several studies addressing persistence found a progressive decrease in adherence with time.

CONCLUSION

Adherence to novel oral therapies is a major issue and further research is warranted to standardize adherence assessment in clinical studies better and to define better the most appropriate approaches to improve long term adherence in oncology practice.

Introduction

The overall rates of patient adherence to long term therapy reach no more than 50% in developed countries [1]. In oncologic diseases, adherence rates are presumed to be higher because of the perceived hazard linked to cancer [2], but published studies have shown conflicting results.

While medical oncologists have treated most of their patients with intravenous (i.v.) cytotoxic drugs, oral therapies have taken an increasing place in the past decade [3–5]. Oral therapy is expected to improve patients' quality of life as it decreases treatment interference with work and social activities, eliminates travel time to an infusion centre as well as the discomfort and potential associated complications of having an i.v. line placed for each administration, and provides a feeling of control over treatment [6, 7]. However, a significant part of the responsibility regarding the management of drug administration and also toxicity is shifted from the oncology team to the patient. This direct involvement in the disease management may be empowering for some patients but overwhelming for others. A recent study revealed that oral cancer treatments are preferred by most of patients due to their convenience but that they are also associated with patients' concerns regarding self-management despite an

erroneous feeling that oral cancer medications are less toxic than i.v. cancer drugs [8]. Indeed, it is currently accepted that all these agents exhibit specific side effects resulting from their interaction with molecular target in normal tissues [9]. Some cancer medications may have a narrow therapeutic index, therefore conferring increased risks of adverse effects [10–13], and oral chemotherapy turns out to be as much at risk as i.v. forms [14]. Unfortunately, the use of oral cancer treatment has expanded more quickly than the infrastructure required to ensure safe care, leading to a new challenge for cancer centres and for patients due to their lack of preparedness for side effects and their unfamiliarity with the possible techniques to mitigate drug toxicity [8]. Additionally, while adjuvant oral hormone therapy for breast cancer contributes to a shift toward a sort of chronic-disease model, most cases of targeted molecular therapy concern patients in a context of palliative and metastatic disease, conferring higher levels of frailty and risks of toxicity. This paradigm shift resulting from the development of oral cancer therapies has made adherence become a major challenge in cancer management.

Recently, the International Society for Pharmacoeconomics and Outcome Research (ISPOR) defined adherence to medications along two dimensions: first, as 'the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency' and second, as the persistence defined as 'the duration of time from the initiation of the medication to discontinuation of therapy' [15]. This definition suggests an alliance between health experts and the patient, the latter undertaking an active role in the treatment decision-making process.

Treatment adherence and its persistence is a complex multifaceted phenomenon that has significant implications for therapeutic success and health-related quality of life. Several factors, intrinsically linked, can affect both adherence and persistence [1, 16–19]. Patient-related factors include sociodemographic characteristics, cognitive impairment, patient outcome expectations and reasons for therapy, lack of understanding regarding self-treatment administration, and features of the illness or potential illness (symptoms, duration, disability, and medically defined seriousness). Among sociodemographic factors, age is a major determinant and the elderly, who account for 45% of all cancers in Europe [20], are known to be particularly vulnerable to adherence concerns. Indeed, the increased number of prescribed medications for multiple comorbid conditions may compromise adherence to treatment due to the confusion between treatment regimens [21, 22]. Moreover, age-related issues, such as visual and cognitive impairment, memory deficits, functional decline, unpleasant side effects, and lack of social support may have a negative impact on adherence [23]. Treatment-related factors include duration, co-administration of other potentially interacting medications, treatment dose timing in relation to food intake, side effects and, in some countries, drug cost [24, 25]. Finally, health system-related factors include availability of the medical staff, clarity and validity of the communication and information provided as well as adequate social, psychological and caregiver support [26]. In a variety of patient populations, non-adherence and non-persistence have been associated with an increased consumption of healthcare resources, including an increased number of physician visits, higher hospitalization rates and longer stays [27–29].

The objective of the present work is to present a state of the art review of the available studies dealing with the adherence of adult patients to oral anticancer treatment. This review addresses the association between assessment methods and measured adherence, discusses the role of putative factors related to adherence, and examines new ways of improving adherence to oral cancer therapies.

Methods

A literature-based search for English-language primary studies published between January 1990 and April 2015 was conducted using the Pubmed electronic database. Studies published since 1990 were selected as that date corresponds to the beginning of oral anticancer medication use and therefore to the emergence of an adherence issue in cancer.

We then conducted a narrative review of based on medical subject heading terms and free-text terms combining concepts related to oral anticancer medication and adherence.

The search has been restricted to studies performed in adults, with adherence measurement as primary outcome.

The search strategy was modelled with the following equation: ('Antineoplastic Agents'[Mesh] OR 'Antineoplastic Agents' [Pharmacological Action] OR 'Neoplasms/drug therapy'[Mesh] OR 'Molecular Targeted Therapy'[Mesh] OR cancer) AND ('Administration, Oral'[Mesh] OR 'oral medication' OR 'oral agent' OR 'oral therapy' OR 'oral treatment' OR 'oral chemotherapy' OR 'oral anticancer') AND ('Medication Adherence'[Mesh] OR 'Patient Compliance'[Mesh] OR adherence OR compliance OR 'non-adherence' OR overadherence).

Forty-eight original articles were identified, half of which having been conducted in the USA and the others in Europe (n = 17), mostly in the UK (n = 7). Most studies included patients with breast cancer, among which 17 were mainly related to hormonal agents used as an adjuvant. Publications dealing with molecular targeted therapies mainly focused on chronic myeloid leukemia (CML) treatments including the tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib and nilotinib. Some studies focused on a particular molecule (essentially capecitabine) in several types of cancer. According to the published data, adherence was assessed either at the time of treatment initiation (25 studies) or during the treatment period (21 studies). Several methods were used to measure adherence (usually until 12 months after treatment initiation) and

persistence (> 12 months). The most represented are based on self-report, a microelectronic device, the Medication Event Monitoring System (MEMS), and prescription refill, these methods being sometimes combined.

Results and discussion

Measured adherence according to assessment methods

Adherence can be assessed by direct and indirect methods [30–32] and self-report medication adherence scales have been recently reviewed [33]. Each method has advantages and limits, and a gold standard still does not exist. The main tools used to assess adherence and their respective features are presented in Table 1.

Individual methods Self-report has been used for adherence assessment to hormone therapy, chemotherapy or molecular targeted therapy especially in breast cancer patients (Table 2 [28, 34–45]). Adherence rates ranged from 38 to 97%.

In studies using MEMS for adherence assessment (Table 3), the mean adherence rates ranged between 74 and 100% [46–52]. Studies assessing the proportion of patients with

Table 1

Advantages, disadvantages and characteristics of adherence assessment methods used in adherence studies in adult cancer patients

	Advantages	Disadvantages	Data collection
Questionnaire	Easy to use	Affected by the Hawthorne effect[a]	Retrospective
	Inexpensive	Can suffer from recall bias	
	Most frequently used	Accuracy tool-dependent	
	Can explore patient's behaviour and beliefs		
Patient interview	Simple	Requires available staff	Retrospective
	Inexpensive	Results depend on interviewer skill and training	
	Can explore patient's behaviour and beliefs	Affected by the Hawthorne effect	
Patient diary	Simple	Affected by the Hawthorne effect (but less than other self- report method)	Prospective
	Inexpensive		
	Provide detailed information		
	Less bias recall	Requires strong individual commitment	
	Provides information about interval intake		
Electronic medication monitors	Provides detailed information	Very expensive	Prospective
		Evaluates cap opening and not drug taking	
		Patients have to take all doses directly into the bottle	
	No bias recall	Can be affected by the Hawthorne effect	
	Provides information about interval intake	Not feasible in clinical practice	
		Intrusive method	
		Useful limited number of patients	
Pill count	Inexpensive	Patients have to return treatment	Retrospective
		Can be affected by the Hawthorne effect	
	Quantifiable	Requires accurate prescription data (fill dates, quantity dispensed)	
	Easy to perform	Time-consuming	
		Not feasible in clinical practice	
Prescription refills	Objective	Surrogate of real adherence	Retrospective
	Provides information on average adherence over time and gap medication supply	Time-consuming	
		Each country has its health system and characteristics	
	Useful for large populations over long term	Variety of databases from only pharmacy data to data sets incorporating electronic medical record	
	Unobtrusive		
	Not affected by the Hawthorne effect	Exclusion of the most non-adherent subjects, those who never filled even one prescription for drug	
Measurement of drug or metabolite level in blood or urine	Objective	Punctual	Retrospective
		Expensive	
		Also influenced by pharmacokinetics	
	Direct proof of drug taking	Assay method not available for many drugs	
		Invasive	
		Can be affected by the Hawthorne effect	

[a]The 'Hawthorne effect' is related to the change of patient behaviour due to the observer effect

adherence rates greater than or equal to a threshold of 80% found rates of 75% to 86%.The only study using pill counts to assess adherence included 25 patients with gastrointestinal or breast cancer treated with capecitabine [53]. Overall adherence was found to be more than 90%. It must be noted that this study included few patients who were followed for a very short time and had been primarily designed to compare two different packagings in terms of adherence, and not to assess overall adherence.

Combination of methods Studies reporting a combination of methods are presented in Table 4 [2, 54–61]. Self-report-based adherence rates ranged between 64% and 100%. Studies using MEMS [2, 54, 55, 60] reported rates between 79 and 92%, which declined to 25% and 49%, respectively, when intake intervals were taken into account. The rates of adherence differed depending on the method used. The most striking difference was reported in the study including 169 patients treated for CML with imatinib [57]. Self-report suggested an adherence rate of 67%, while pill counts found only 14% of perfectly adherent patients. However, in other studies based on patient or physician reviews as well as on urine analysis [58], or on both patient diary and MEMS [55], the rates were found to be similar.

Database (prescription refill) Table 5 shows adherence rates when databases were used for assessment [62–81]. Twenty studies, mostly performed in breast cancers or leukaemia, were based on prescription refill from assurance databases. One of the largest ones was conducted in more than 10 000 patients regardless of cancer site or oral therapy [76]. All these studies allowed the assessment of the persistence of adherence over several years.

Table 2

Design and main results of studies using self-report for adherence assessment

Authors [reference]/ Year/Country/ Subject number	Cancer site	Oral therapy	Measurement method	Adherence/persistence definition	Adherence/ persistence rate (% of patients)	Assessment period
Atkins *et al.* [34]/2006/UK/131	Breast	Tamoxifen, anastrozole, capecitabine	Patients interview	Reports neither forgot nor chose not to take their medication	43.5% 46% with tamoxifen 39% with anastrozole	Single point
Barthélémy *et al.* [35]/2015/France/201	Solid and and haematologic	Oral anticancer medication, targeted therapy or hormone/ chemotherapy	15-item questionnaire	Reports never forgotten nor voluntarily not taken treatment or reduced dosing during the past month	72.5% with targeted therapy and 69.6% with hormone/chemotherapy	11 months
Bhattacharya *et al.* [36] /2012/UK/43	Breast and colorectum	Capecitabine	MARS-5 questionnaire	Score = 25 (from 5 to 25)	76.7%	Single point
Demissie *et al.* [37]/2001/USA/189	Breast	Tamoxifen	Patient interview	Reports taking tamoxifen at any time during the study period	85%	15 months
Fink *et al.* [38]/2004/USA/516	Breast	Tamoxifen	Patient interview	Reports always taking tamoxifen	96.3% at baseline 89% at 1 year 83% at 2 year	2 years
Grundfeld *et al.* [39]/2005/UK/110	Breast	Tamoxifen	Single question	Reports taking tamoxifen everyday in past week	88%	Single point
Jonsson *et al.* [40]/2011/Sweden/38	CML	Imatinib	MMAS-9 questionnaire	Score > 10 (from 1 to 13)	97%	Single point
Kimura *et al.* [41]/2014/Japan/172	All	Oral anticancer medication	27-item questionnaire	Good medication adherence if score ≥ 4 (from 1 to 5)	Good adherence for 64%	Single point
Lash *et al.* [42]/2006/USA/462	Breast	Tamoxifen	Patient interview	Reports not stop taking tamoxifen	69%	5 years
Lebovits *et al.* [28]/1990/USA/51	Breast	Cyclophosphamide and/or prednisone	Patient interview	Dosage adherence: > 90% of prescribed doses taken Behavioural adherence: 90% to 110% of prescribed doses taken	57% 53% 23% were overadherent	6 months
Murthy *et al.* [43]/2002/India/53	Breast	Tamoxifen	Questionnaire	Reports not missing a single dose	38% (24% missed ≥1 dose/week)	6 months
Ruddy *et al.* [44]/2012/USA/133	Breast	Cyclophosphamide	Patient diary	Reports taking ≥80% of prescribed doses	Average 97% 95%	6 cycles
Winterhalder *et al.* [45]/2011/Switzerland/177	Breast and GIST	Capecitabine	Patient diary	Reports taking recommended dosage and respect intake interval	91%	Mean of 6.3 months

MARS-5: 5 items medication adherence report scale. CML: Chronic myeloid leukemia. MMAS-9: 9 items Morisky Medication Adherence Scale. GIST: gastrointestinal stromal tumors

Table 3

Design and main results of studies using only the Medication Event Monitoring System (MEMS) for adherence assessment

Authors [reference]/ Year/Country/ Subject number	Cancer	Oral therapy	Adherence/persistence definition	Adherence/persistence rate (% of patients)	Assessment period
Lee *et al.* [46]/1992/UK/21	Lymphoma	Chlorambucil, cyclophosphamide, prednisone, dexamethasone		Mean : 100% ± 20.6%	1 to 4 cycles
Lee *et al.* [47]/1993/UK/12	Small cell lung cancer	Etoposide		Mean : 93.2% ± 12%	1 to 3 cycles
Lee *et al.* [48]/1996/UK/11	Ovarian cancer	Altretamine		Mean : 97.4% ± 6.9%	1 to 5 cycles
Marin *et al.* [49]/2010;	CML	Imatinib		Median: 98% (range 24–104%)	3 months
Ibrahim *et al.* [50]/ 2011/UK/87			Doses taken ≥90% of prescribed doses	73.6%	
			Doses taken ≥80% of prescribed doses	86%	
Partridge *et al.* [51]/ 2010/USA/150	Breast cancer	Capecitabine	Doses taken ≥80% of prescribed doses	75% including 11% of overadherent patients	126 days
			Overadherent : > 100%	Mean : 78%	
Timmers *et al.* [52]/ 2015/The Netherlands/62	Non-small cell lung cancer	Erlotinib	Proportion of days covered	Mean 96.8 ± 4%	4 months

In seven studies assessing hormone therapy for breast cancer, adherence was defined as a medication possession ratio (MPR) reaching at least 80% [70, 71, 73–75, 77, 78]. Persistence rates ranged from 63% to 81% at 1 year and from 55% to 75% at 2 years. Four studies [63, 70, 71, 78] considering non-adherence when the interval between refills was higher than 180 days showed adherence rates ranging from 78% to 85% at 1 year, which decreased to 72% to 78% at 2 years, to reach 29% to 68% at 5 years. Three studies conducted in breast cancer considered non-adherence as an interval between refills greater than 60 [71, 72] or 90 [77] days. Adherence rates were around 80% at 1 year [71, 77], but fell to 27% [71] and 51% [72] at 5 years.

Eight studies had enrolled patients treated for CML with TKIs [62, 64–66, 68, 79–81] including imatinib [62, 64, 66, 79], and dasatinib or nilotinib [62, 68, 80, 81]. In one study addressing patient adherence to imatinib, treatment interruptions defined as failure to refill imatinib within 30 days from the run-out date of the prior prescription were reported in 31% of patients [64]. Another study defining non-adherence as an unwarranted treatment interruption for more than 1 week found a similar rate of non-adherent patients [66]. When non-adherence was defined as a MPR lower than 85%, the rate was around 40% [70]. In two studies assessing adherence to dasatinib and nilotinib [68, 80], the average MPRs were around 70% and 80%, respectively. In 137 patients treated with TKIs, mean MPRs were higher than 85% but the rates of total adherence at baseline and after 12 months were only 24% and 18%, respectively. Moreover, the authors underlined that the MPR was the most effective method to evaluate adherence compared with the Morisky Medication Adherence Questionnaire and with the medication diary [65].

In a large study including 10 508 patients who received newly prescribed oral oncolytic therapy for various types of tumours [76], the abandonment rate (no prescription refill or since prior prescription greater than 90 days) was only 10%.

Finally, a study among 1400 patients treated with bicalutamide for prostate cancer [67] reported a 60% rate of adherent patients (MPR greater than 80%) with 10% of patients being found to have very poor adherence (MPR lower than 50%).

Factors related to adherence rate variability

Adherence definition and measurement time modality The discrepancies between reported studies may have several explanations. First, there was no consensual definition of adherence, even for a same method of assessment, which hinders the interpretation of data and represents the main limitation for a comparison between studies. Indeed, two main types of definitions were used. The first one corresponded to a coverage of at least 80% of days with drug available, while the second one included a tolerated length of interruptions during the treatment period (1 to 180 days). Moreover, according to the time of collection of the primary outcome (between 1 and 5 years), adherence parameters referred to adherence and/or persistence. In this respect, all studies addressing adherence or persistence rates during several years, with several points of data collection, found a progressive decrease due to a lapse of time since treatment initiation. In studies using self-report, some evaluation was performed 6 months [28, 43, 44], 15 months [37], 2 years [38] or 5 years [42] after treatment initiation, while in others, it was assessed at a given time (all patients having not experienced the same duration of treatment) [34, 36, 39, 40]. Because of these methodological differences, no general rule is deductible and no gold standard is acknowledged to assess adherence, even when considering the same treatment in the same pathology.

Table 4

Design and main results of studies using several combined methods for adherence assessment

Authors [reference]/ Year/Country/ Subject number	Cancer	Oral therapy	Method of measure	Adherence/persistence definition	Adherence/persistence rate (% of patients)	Assessment period
Klein *et al.* [54]/2006/USA/90	Myelo-dysplastic syndrome	Topotecan	Pill count	Doses taken = 100% of prescribed doses	89,5%	5–10 days
			MEMS	Doses taken = 100% of prescribed doses	92.5%	
				All doses taken on prescribed dosing interval (± 2 h)	49%	
Mayer *et al.* [55]/2009/USA/18	Breast cancer	Capecitabine, gefitinib	Patient diary		Median : 96% for gefitinib Median : 97% for capecitabine	2 cycles
			MEMS		Median : 99% for gefitinib Median : 96% for capecitabine	
Mazzeo *et al.* [56]/2011/Belgium/28	GIST	Imatinib	BAAS questionnaire	Reports taking recommended dosage and respect intake interval (± 2 h)	71% at baseline 76% at 3 months	3 months
			Patients' VAS		Mean : 96.6% at baseline Mean : 95.4% at 3 months	
			Physicians' VAS		Mean : 97.1% at baseline Mean : 95.2% at 3 months	
			Caregivers' VAS		Mean : 97.3% at baseline Mean : 96.8% at 3 months	
Noens *et al.* [57]/2009/Belgium/ 169	CML	Imatinib	BAAS questionnaire	Reports taking recommended dosage and respect intake interval (± 2 h)	63.9% at baseline 67.3% at 3 months	3 months
			Patients' VAS		Mean : 95.3% at baseline Mean : 95.7% at 3 months	
			Physicians' VAS		Mean : 94.9% at baseline Mean : 94.9% at 3 months	
			Caregivers' VAS		Mean : 97% at baseline Mean : 97.1% at 3 months	
			Pill count	Doses taken =100% of prescribed doses	Mean : 90.9% at 3 months 14.2% 71% were under-adherent 14.8% over-adherent	
Sadahiro *et al.* [58]/2000/Japan/72	Colorectal cancer	Uracil tegafur	Patient interview	NS	89% at 3 months, 91% at 6 months, 93% at 9 months and 91% at 1 year	1 year
			Physician interview	Omission <3 doses/week	94% at 3 months, 95% at 6 months, 98% at 9 months and 94% at 1 year	
			Urine analysis	Urine tegafur concentration ≥ 3500 ng ml^{1}	94.7%	
Timmers *et al.* [59]/*2014/The Netherlands/216*	All	Oral anticancer medication	Telephonic pill count Questionnaire Patient's medical file Pharmacy medication record	Adherence rate expressed as the % of doses taken (/prescribed) and calculated by means of the so-called Patient's files-Pharmacy record- Pill count method (PPP method) (obtained for 177 patients)	Mean: 99.1% ± 95.4% (34.4% having an adherence rate of exactly 100%; 20,3% an adherence rate range ≤ 95% - ≥105%; 63,9% showing under-consumption	17 months
Walter *et al.* [60]/2014/Canada/19	GIST	Capecitabine	Self-report Pill count MEMS	Doses taken ≥80% of prescribed doses	99% 100% 61%	3 months
Waterhouse *et al.* [2]/1993/USA/26	Breast cancer	Tamoxifen	Questionnaire	Doses taken ≥80% of prescribed doses	100% Mean : 97.9% ± 3%	Mean of 2.92 months

(Continues)

Table 4
(Continued)

Authors [reference]/ Year/Country/ Subject number	Cancer	Oral therapy	Method of measure	Adherence/persistence definition	Adherence/persistence rate (% of patients)	Assessment period
			Pill count	Doses taken ≥80% of prescribed doses	83.3% Mean : 92.1% ± 9.8%	
			MEMS	Doses taken ≥80% of prescribed doses	79.2%	
				No dosing-interval errors (± 3 h)	75%	
				Doses taken ≥80% of prescribed doses and no dosing-interval errors (± 3 h)	25%	
Ziller *et al.* [61]/2009/ Germany/100	Breast cancer	Tamoxifen, anastrozole	Questionnaire	Reports taking recommended dosage and respect intake interval	100%	NS
			Prescription refill records	MPR ≥ 80%	80% for tamoxifen 69% for anastrozole	

MEMS: Medication Event Monitoring System. GIST: gastrointestinal stromal tumours. BAAS: Basel Assessment of Adherence Scale with Immunosuppressive Medication adapted to imatinib. VAS:visual analogue scale. NS: not specified in the publication

Choice of the method and intent Nowadays, there is still a lack of validated tools to assess patient adherence with medications, especially in oncology. Indeed, even self-report methods differ from one study to another. Five studies used patients' interviews [28, 34, 37, 38, 42], and one study assessed adherence through patient diaries, which investigated both dosage and intake intervals [45]. Other studies used a self-administered questionnaire either homemade [39, 43] or consisting in validated MMAS-9 [40] or MARS-5 [36] questionnaires. These questionnaires only assessed the notion of treatment forgetting, and did not take into account a possible over-adherence or drug taking modalities. Furthermore, the use of different time scales, from a 24 h recall to a global self-report over several months, makes the combination of data across measures difficult. In terms of feasibility for clinical practice, adherence exploration should preferentially be based on self-report.

The three studies using MEMS included very few patients [46-48], with one being part of a clinical trial [48]. Besides, the excellent rates of adherence reported in these studies were based on average rates of adherence, while adherence assessment usually consists in evaluating the proportion of patients with adherence rates greater than or equal to a predefined threshold (usually 80% or 90%). Thus, the average rates may be expected to be deceptively high with a number of very few adherent patients. Furthermore, adherence was not assessed over long periods (4 months maximum [51, 52]), even in the case of long term therapy with imatinib [49, 50]. Finally, the main advantage of MEMS is to provide information on the time of dosing, although most studies did not exploit these results.

In studies using a combination of several assessment methods, two new tools were used. Two studies used the self-report validated Basel Assessment of Adherence Scale (BAAS) questionnaire adapted to imatinib and a visual analogue scale submitted either to the patient himself, to the physician or to the caregiver [56, 57]. Hence, recent reviews found a tremendous variability of adherence rates to oral anticancer medication depending on measurement methods [82, 83]. Although using a multi-method should be considered more powerful, it increases the complexity of both the analysis and the interpretation. Furthermore, these methods often used different time scales and did not report unitary rates of adherence, which makes the comparison difficult. In addition, some studies gave merely raw results from different tools but did not really compare and interpret them. In this respect, the construction of a composite adherence score by combining measures may maximize accuracy and then permit a better evaluation of adherence and identification of possible barriers [59, 60, 84]. In the future, second generations of electronic medication adherence monitors may be expected to provide real-time adherence monitoring even though their feasibility, validity and acceptability remain to be established. The failure to find a panacea should lead each medical team to choose the most appropriate adherence assessment tool in accordance with their needs (research or clinical practice and resource), which should be specially tailored to the treatment profile and the therapeutic objectives.

Patient-related factors Patient awareness that adherence is being measured may impact on the degree of adherence, and patients who are cognizant of ongoing observation may demonstrate an improved behaviour. The change of patient behaviour due to the observer-effect is termed the 'Hawthorne effect' [19, 85]. This confounding event is expected to occur with most assessment methods (except prescription refill) to various extents, leading to an over-estimated adherence. For instance, the Boolean questions (yes/no) of the self-report method are likely to be affected by the Hawthorne effect.

Table 5

Design and main results of studies using prescription refill for adherence assessment

Authors [reference]/ Year/Country/ Subject number	Cancer	Oral therapy	Adherence/persistence definition	Adherence/persistence rate (% of patients)	Assessment period
Anderson *et al.* [62]/2015/Canada/124	CML	Imatinib, dasatinib, nilotinib	MPR ≥ 80%	Median MPR : 95% (interquartile ranges 83.0–107); MPR < for imatinib (/dasatinib or nilotinib)	18 months (> 6 months)
Barron *et al.* [63]/2007/Ireland/2816	Breast	Tamoxifen	Interval between refills ≤180 days	77.9% at 1 year 71.6% at 2 years 64.8% at 3.5 years	3.5 years
Darkow *et al.* [64]/2007/USA/267	CML	Imatinib	Interval between refills ≤30 days	69% Mean MPR : 77,7%	1 year
de Almeida *et al.* [65]/2013/Brazil/137	CML	Tyrosine kinase inhibitors	NS	Mean MPR: 89% at baseline 91% at 6 months 90% at 12 months	Median of 337 days
Ganesan *et al.* [66]/2011/India/516	CML	Imatinib	Interval between refills ≤1 week	70.4%	Mean of 38.9 months
Grundmark *et al.* [67]/2012/Sweden/1406	Prostate	Bicalutamide	MPR ≥ 80%	60%	1 year
Guerin *et al.* [68]/2012/USA/878	CML	Dasatinib Nilotinib	NS	Mean MPR : 73.9 ± 24.6% for dasatinib 80 ± 24.6% for nilotinib	1 year
Guth *et al.* [69]/2008/Switzerland/287	Breast	Hormone therapy tamoxifen, exemestane, anastrozole, and letrozole	NS	89.2%	5 years
Hershman *et al.* [70]/2010/USA/8769	Breast	Hormone therapy tamoxifen, exemestane, anastrozole, and letrozole	MPR ≥ 80% Interval between refills ≤180 days	72% 68%	4.5 years
Nekhlyudov *et al.* [71]/2011/USA/1408	Breast	Hormone therapy tamoxifen, exemestane, anastrozole, and letrozole	Interval between refills ≤60 days Interval between refills ≤180 days MPR ≥ 80%	79% at 1 year 70% at 2 years 62% at 3 years 53% at 4 years 27% at 5 years 85% at 1 year 78% at 2 years 71% at 3 years 62% at 4 years 29% at 5 years 78.4% at 1 year 75.2% at 2 years 61.7% at 5 years	5 years
Owusu *et al.* [72]/2008/USA/96	Breast	Tamoxifen	Interval between refills ≤60 days	51%	5 years
Partridge *et al.* [73]/2003/USA/2378	Breast	Tamoxifen	MPR ≥ 80%	77% at 1 year Mean MPR : 87% at 1 year 68% at 2 years 61% at 3 years 50% at 4 years	4 years
Partridge *et al.* [74]/2008/USA/1498 (plan A)	Breast	Anastrozole	MPR ≥ 80%	81% at 1 year Mean MPR : 88% at 1 year Patients with 3 years follow-up : 78% at 1 year 72% at 2 years 68% at 3 years	3 years

(Continues)

Table 5
(Continued)

Authors [reference]/ Year/Country/ Subject number	Cancer	Oral therapy	Adherence/persistence definition	Adherence/persistence rate (% of patients)	Assessment period
Id/1899 (plan B)			MPR ≥ 80%	72% at 1 year Mean MPR : 82% at 1 year Patients with 3 years follow-up : 69% at 1 year 55% at 2 years 50% at 3 years	
Id/8994 (plan C)			MPR ≥ 80%	78% at 1 year Mean MPR : 86% at 1 year Patients with 3 years follow-up : 74% at 1 year 62% at 2 years 60% at 3 years	
Sedjo *et al.* [75]/2011/USA/13 593	Breast	Aromatase inhibitors exemestane, anastrozole, and letrozole	MPR ≥ 80%	77%	1 year
Streeter *et al.* [76]/2011/USA/10 508	All	All	Interval between refills ≤90 days	90%	NS
Weaver *et al.* [77]/2013/USA/857	Breast	Hormone therapy tamoxifen, exemestane, anastrozole, and letrozole	MPR ≥ 80% Interval between refills ≤3 months	63% at 1 year 62% at 2 years 60% at 3 years 55% at 4 years 46% at 5 years 82% at 1 year	5 years
Wigertz *et al.* [78]/2012/Sweden/1741	Breast	Hormone therapy tamoxifen, exemestane, anastrozole, and letrozole	MPR ≥ 80% and interval between refills ≤180 days Interval between refills ≤180 days MPR ≥ 80%	69% 88% 80%	3 years
Wu *et al.* [79]/2010/USA/592	CML	Imatinib	MPR ≥ 85%	59.1%	1 year
Wu *et al.* [80]/2010/USA/521	CML	Dasatinib, nilotinib	NS	Mean MPR : 69% for dasatinib 79% for nilotinib	6 months
Yood *et al.* [81]/2012/USA/2064	CML	Dasatinib, nilotinib	MPR ≥ 85%	Calculated hazard ratios for poor adherence of nilotinib *vs.* dasatinib : 1,6 [1.0–2.4]	276 days (dasatinib) 170 days (nilotinib)

CML: chronic myeloid leukemia. MPR: Medication Possession Ratio. NS: not specified in the publication

Patients by themselves may reduce or modulate drug dosage or scheduling due to side effects, perceived unresponsiveness, unrecognized depression or, paradoxically, because of a false sense of security in case of disease response, without informing their oncologist or health-care practitioner. According to a recent study exploring perceptions and experiences of patients receiving oral chemotherapy [9], patients indicated that their concerns during the stages of the medication process included a lack of preparedness to manage and/or alleviate side effects, challenges for obtaining medications through retail pharmacies and uncertainty around proper administration of oral medication.

Patient data available from reported studies do not allow the identification of patient-related subtypes including age or health literacy, which are probably essential determinants for adherence. Factors influencing adherence in patients taking oral anticancer agents have been recently reviewed [86–88]. The American Society of Clinical Oncology (ASCO) and the Oncology Nursing Society (ONS) have recently updated their chemotherapy administration safety standards and specifically address the issues associated with oral chemotherapy [89]. Assessment of adherence should include the verification that the patient understands how

to take the prescribed regimen and what to do in case of a missed dose. Inquiry regarding access to oral agents and their related costs should also be conducted [89].

Study limitations

Several limitations of this review should be noted. The studies selected for the analysis used different measures of adherence including questionnaires or microelectronic devices in disparate populations in terms of characteristics, disease and treatment. Major differences in factors influencing adherence may then be expected in the different populations. While a major strength of our approach is the variety of publications, it may be limited due to this heterogeneity. The difficulty to perform a clear identification of adherence determinants makes the distinction across studies complicated and hinders an in-depth comparison and analysis, leading to a thorough but narrative review.

Non-adherence was relatively common across studies. In accordance with those previously reported, our review does not allow to point out other pertinent factors that might influence adherence. In this respect, disease-related determinants such as cancer localization, treatment protocol and stage of the disease might have been particularly relevant.

More research is needed to investigate better which factors may influence cancer patients' adherence to their oral therapies. Inhibiting factors may be helpful to clinicians to identify better patients at increased risk for non-adherence. Identification of determinants associated with improved adherence can be incorporated into interventions aimed to promote patients' adherence. Beside patient-related factors, adherence rate discrepancies were found to be dependent on the assessment method used and on the timing of the measurements.

Due to the lack of reliable and validated measurement methods, comparisons across studies remain arduous and further research is needed to establish a consensus for standardized measurement tools which could be generalized to clinical settings, and then be useful for both patients and providers.

Area for adherence improvement

In order to optimize adherence, it is imperative to improve patients' education and to encourage more frequent follow-up by healthcare providers during the course of therapy [35, 90]. In routine practice, adherence should not be presumed and oncologists should monitor patients for adherence by employing a strategy based on open questions about medication-taking behaviour [91]. Clinicians should develop skills in customizing the regimen to the patient's life-style taking into account the issues related to comorbidities and polypharmacy [92]. It seems essential to evaluate first patient reliability and to avoid prescribing oral treatment to patients with socioeconomic and medical conditions which may predict poor adherence. Patients with oropharyngeal disability, gastrointestinal problems, depression, unreliable behaviour, lack of motivation in the past or history of self-modulating doses of other medications are frailest and need more attention. Then, health staff have to be aware of these adherence issues in order to identify potential non-adherent patients and implement possible effectiveness interventions to encourage an accurate self-administration of oral therapies, like daily pill boxes, medication diaries, nurse or pharmacist consultations [93]. Discussing the importance of adherence with the patients may be beneficial to help those with poor adherence to improve, and to encourage those with good adherence to carry on. Furthermore, an improved dosing of pills, an appropriate education about the importance of adherence and good communication may increase adherence rates [90]. The latter should integrate an emphasis on the expected benefits of the prescribed regimen as well as the promotion of medication-taking systems, and should include caregiver assistance to favour patient involvement and motivation and reinforce desirable behaviour.

Finally, health staff have to educate patients about these matters, and community pharmacist involvement may be essential in achieving adherence in the ambulatory setting [94, 95]. Interventions aimed to enhance patient adherence to prescriptions may be educational, behavioural, affective or multidimensional [35, 96].

Conclusion

Adherence and persistence to oral therapies are a major issue, especially regarding the respect of taking plan and modalities. Despite the increased use of oral chemotherapy, the number of studies addressing the issue of adherence remains surprisingly low. So far, very little data have been published on adherence and persistence to oral molecular targeted therapies in solid malignancies. Therefore, new research is needed to investigate the rates of adherence and persistence with these new oral targeted therapies and to standardize adherence assessment in clinical studies better. Moreover, it appears important to address the consequences, especially in terms of outcome impairments, of missed or extra doses, time lag in dose timing and/or drug taking modalities.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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